WO 2005/085245 PCT/GB2005/000885

CLAIMS:

1. A compound of formula (I):

$$R^{1'} \xrightarrow{X_2} \xrightarrow{X_1} \xrightarrow{N} \xrightarrow{N} O$$

$$R^{1'} \xrightarrow{X_2} \xrightarrow{X_3} \xrightarrow{X_4} \xrightarrow{N} \xrightarrow{N} O$$

Ι

or a pharmaceutically acceptable salt thereof, wherein:

one of X_1 , X_2 , X_3 and X_4 is N and the others are C;

Y is -C(O)-, $-S(O)_2$ -, or -C(NH)-;

Z is C_{1-4} alkylene, oxygen, - $(CH_2)_mO$ -, - $O(CH_2)_m$ -, -NR-, - $(CH_2)_mNR$ -, - $NR(CH_2)_m$ -, - $(CH_2)_mS(O)_2$ -, or a bond;

m is 1, 2, 3, or 4;

R is C₀₋₄alkyl, C₀₋₄alkylaryl, or C₀₋₄alkylhetaryl;

R¹ and R¹ are each independently, halogen, hydroxy, cyano, C₀₋₄alkyl, C₁₋₄alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

 R^2 is C_{0-4} alkyl, $COOR^6$, COR^6 , C_{1-4} alkoxy C_{1-4} alkyl-, hydroxy C_{1-4} alkyl-, cycloalkyl C_{0-4} alkyl-, aryl C_{0-4} alkyl-, or hetaryl C_{0-4} alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $-N(C_{0-4}$ alkyl)(C_{0-4} alkyl), $-SO_2C_{1-4}$ alkyl, $-SO_2N(C_{0-4}$ alkyl)(C_{0-4} alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

 R^3 is hydrogen, $-COOC_{0-4}$ alkyl, C_{1-4} alkoxy, C_{1-4} alkyl, aryl C_{1-4} alkylthio—, $-C_{0-4}$ alkylaryl, $-C_{0-4}$ alkylhetaryl, $-C_{0-4}$ alkylcycloalkyl, or $-C_{0-4}$ alkylheterocyclyl, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, C_{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, $-C_{0-4}$ alkylNHC(O)O(C_{1-4} alkyl), $-C_{0-4}$ alkylNR 7 R 8 , -C(O)R 9 , C_{1-4} alkoxy C_{0-4} alkyl—, $-COOC_{0-4}$ alkyl, $-C_{0-4}$ alkylNHC(O)R 9 , $-C_{0-4}$ alkylC(O)N(R 10)₂, $-C_{1-4}$ alkoxy C_{1-4} alkoxy, hydroxy C_{0-4} alkyl—, $-NHSO_2R^{10}$, $-SO_2(C_{1-4}$ alkyl), $-SO_2NR^{11}R^{12}$, 5- to 6-membered heterocyclyl, phenyl C_{0-2} alkoxy, or phenyl C_{0-2} alkyl substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $-N(C_{0-4}$ alkyl)(C_{0-4} alkyl), $-SO_2C_{1-4}$ alkyl, $-SO_2N(C_{0-4}$ alkyl)(C_{0-4} alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

or R^3 is $-NR^4(-C_{0-4}alkylR^5)$;

 R^4 is C_{0-3} alkyl, $-C_{2-3}$ alkyl- NR^7R^8 , C_{3-6} cycloalkyl optionally substituted by hydroxy C_{0-4} alkyl—further optionally substituted by hydroxy, C_{1-2} alkoxy C_{2-4} alkyl—, or C_{1-2} alkyl— $S(O)_n$ — C_{2-3} alkyl—;

n is 0, 1, or 2;

 R^5 is hydrogen, hydroxy C_{2-3} alkyl-, C_{1-2} alkoxy C_{0-4} alkyl-, or aryl, hetaryl, or heterocyclyl;

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wherein a heterocyclic nitrogen-containing R^5 ring optionally is mono-substituted on the ring nitrogen with C_{1-4} alkyl, benzyl, benzoyl, C_{1-4} alkyl-C(O)–, $-SO_2C_{1-4}$ alkyl, $-SO_2N(C_{0-4}$ alkyl)(C_{0-4} alkyl), C_{1-4} alkoxycarbonyl, or aryl(C_{1-4} alkoxy)carbonyl; and wherein the R^5 rings are optionally mono-substituted on a ring carbon with halogen, cyano, C_{1-4} alkyl-C(O)–, C_{1-4} alkyl- SO_2 –, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, $-N(C_{0-4}$ alkyl)(C_{0-4} alkyl), hydroxy C_{0-4} alkyl-, or C_{0-4} alkylcarbamoyl–, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

 R^6 is C_{1-4} alkyl, aryl, or hetaryl;

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R⁷ and R⁸ are independently C₀₋₄alkyl, C₃₋₆cycloalkyl, or CO(C₁₋₄alkyl);

R⁹ is C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R¹⁰ is C₀₋₄alkyl, or C₃₋₆cycloalkyl; and

 R^{11} and R^{12} are independently C_{0-4} alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R³.

- 2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X_3 is N.
- 3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X_1 is N.
- 4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)- or $-S(O)_2$ -.
- 5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is C_{1-4} alkylene, oxygen, $-(CH_2)_mO$ -, -NR- or a bond.
- 6. A compound according to any one of the preceding claims 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and $R^{1'}$ are each independently, hydrogen or halogen.
- 7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^1 is hydrogen and the other is 5-chloro.
- 8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.
- 9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, -NR⁴R⁵, -NR⁴(-C₁₋₄alkylR⁵), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as defined in claim 1.
- 10. A compound of formula (I) as defined in any one of Examples 1 to 25, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

- 12. A method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 13. A method for the treatment of hyperglycemia or diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 14. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 15. A method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 16. A compound of formula (IV):

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 $R^{1'} \xrightarrow{X_2} \xrightarrow{X_1} \xrightarrow{X_1} \xrightarrow{N} O$ $R^{1'} \xrightarrow{X_2} \xrightarrow{X_3} \xrightarrow{X_4} \xrightarrow{N} O$ IV

wherein R^1 , R^1 , R^2 , X_1 , X_2 , X_3 and X_4 are as defined in claim 1, or a protected derivative thereof.